REMARKS

Applicant respectfully requests reconsideration. Claims 30-41, 70-74 and 80-83 were previously pending in this application. Claim 30 has been amended to incorporate the feature of claim 31. Claim 31 has been canceled. As a result, claims 30, 32-41, 70-74 and 80-83 are pending for examination. No new matter has been added.

Applicant submits herewith a Declaration from Dr. Erwin Sablon in support of patentability of the claims as presented. Dr. Sablon is an expert in molecular DNA and RNA engineering and microbial expression technology, and was active in these fields before, during and after the time that this application was filed.

Objection for Priority of Claim 34

Applicant acknowledges that the foreign priority date is not granted for claim 34.

Rejections Under 35 U.S.C. § 102

The Examiner has maintained the rejection of claims 30-36, 39, 74, 80, and 83 under 35 U.S.C. § 102(e) as being anticipated by Graham (US Patent 6,573,099) for reasons of record as set forth in the Office action mailed on December 7, 2009. Applicant respectfully requests reconsideration of the rejection.

As currently amended, the claimed invention comprises an expression vector that comprises promoters flanking a DNA sequence such that the promoters initiate transcription of said DNA sequence to produce double stranded RNA upon binding of a transcription factor to said promoters, whereby said double stranded RNA is produced in said micro-organism, in which said expression vector comprises two identical promoters flanking said DNA sequence. (emphasis added) The

Examiner admits on page 3 of the Office Action that "Graham discloses 'two copies' of a structural gene sequence." But the Examiner also states that "the word [*sic*] 'two copies' does not indicate that the sense orientation copy and the antisense orientation copy are ***not*** contiguous so as to form a single, one DNA 'sequence'." (emphasis in original)

Respectfully, this statement of the Examiner is not in agreement with the disclosure of Graham. In column 2, Graham provides three aspects of the invention relating to synthetic genes. In the first aspect, the synthetic gene comprises a structural gene sequence placed under the control of a promoter. In the second aspect, the synthetic gene comprises multiple structural gene sequences placed under the control of a single promoter. In the third aspect, the synthetic gene comprises multiple structural gene sequences, wherein each of the structural gene sequences is placed under the control of a promoter.

Applicant notes that a "multiple structural gene sequence" is further defined in Graham at col. 10, lines 1-4 as comprising "a tandem repeat or concatamer of two or more identical nucleotide sequences or alternatively, a tandem array or concatamer of non-identical nucleotide sequences". This is expanded upon at col. 11, lines 3-8: "The individual structural gene units of the multiple structural gene ... may be spatially connected in any orientation relative to each other, for example head-to-head, head-to-tail or tail-to-tail...." Col. 11, lines 47-50 further clarifies that the individual structural genes may be spatially separated by placing a linker or a "stuffer fragment" between the individual genes.

Thus a "multiple structural gene sequence" driven by more than one promoter cannot be a single sequence set between two promoters.

At col. 7, lines 15-18, Graham states that the invention includes synthetic genes in which the structural gene component is "operably connected in the sense or antisense orientation to a promoter sequence". (emphasis added) Thus Graham teaches the linkage of genes to a promoter in a sense **or** antisense orientation, but not the linkage of a gene sequence in both sense and antisense

orientations, with promoters flanking a DNA sequence such that the promoters initiate transcription of said DNA sequence to produce double stranded RNA, as is recited in the claimed invention.

The Examiner argues on page 4 of the Office Action that Graham "encompasses" a structure that comprises 5'-3': promoter 1, copy 1 of structural gene sequence in sense orientation, copy 2 of structural gene sequence in antisense orientation, promoter 2. But the Examiner's assertion is not based on any citation to the Graham patent. Applicant respectfully requests that the Examiner provide a factual basis in the Graham patent for the asserted structure attributed to the Graham patent.

In fact, even Graham constructs that could meet the Examiner's assertion do not meet the other requirements of the claimed invention. For example, Fig. 21 shows a plasmid in which structural gene sequences can be placed between two promoters (CMV-IE and SV40 late promoter). However, as described in col. 19 and col. 20, this plasmid allows "the CMV-IE **or** the SV40 late promoter" to drive transcription of a structural gene or multiple structural genes "in the sense **or** antisense orientation". (emphasis added) Graham also states unequivocally at col. 20, lines 4-10 that "In order for expression of a structural gene sequence to occur from this plasmid, it must be introduced with its own transcription termination sequence located at the 3' end, because there are not transcription termination sequences located between opposing CMV-IE and SV40 late promoter sequences in this plasmid." This makes it clear that the promoters are not flanking "a DNA sequence" as recited in the instant claims. Moreover, this embodiment of Graham also does not meet the recitation that the promoters are identical.

Accordingly, Applicant submits that the Graham patent does not provide all of the elements of the claimed invention arranged as in the claim. MPEP 2131.

Rejections Under 35 U.S.C. § 103

1. The Examiner has maintained the rejection of claims 30-41, 70-74, and 80-83 under 35 U.S.C. § 103(a) as being unpatentable over Timmons et al., McAllister et al., Conkling et al., and Talkad et al. for the reasons of record as set forth in the Office action mailed on December 7, 2009 and as stated in the Office Action. Applicant respectfully traverses the rejection.

The cited combination of references does not provide all of the elements of the claimed invention

McAllister provides plasmids that contain an improved T3 promoter in combination with either a SP6 promoter (plasmid pJFK15) or a T7 promoter (plasmid pJFK16). The T3/SP6 or T3/T7 promoter pairs flank a polylinker segment into which a DNA fragment of interest is placed. As described by McAllister, this DNA fragment is "to be transcribed" (col. 2, lines 22-23) to "synthesize RNA probes of high sensitivity" (col. 3, lines 44-46). The purpose of these vectors is further emphasized in claim 7: "...the recombinant DNA vector being capable of transcription of DNA to produce RNA strands complementary to either one of the strands of the inserted DNA sequence when there is supplied to the vector a phage promoter-specific polymerase..." (emphasis added). Similarly in claim 13, McAllister emphasizes the use of the vectors: "A kit for genetic applications especially for transcription of DNA to synthesize RNA transcripts complementary to either strand of a DNA sequence..."(emphasis added). At the time of filing of the application, McAllister would have be read by the skilled person as teaching a dual promoter vector for synthesizing either strand of a DNA insert, but not both strands at one time.

Applicant provides herewith a Declaration from Dr. Erwin Sablon, in which *inter alia* the use of vectors as described in McAllister is discussed.

According to Dr. Sablon, the McAllister et al. patent describes vectors contain a multiple cloning site flanked by two phage RNA polymerase promoters positioned to express either strand of a DNA molecule inserted in the multiple cloning site, which vectors have SP6 and T3 bacteriophage promoters or T7 and T3 bacteriophage promoters. (Declaration of Dr. Sablon at ¶ 7.) These vectors are used for *in vitro* transcription of RNA of one strand of a DNA sequence, such as for making RNA probes. (Declaration of Dr. Sablon at ¶ 8.) Dr. Sablon references claim 7 of the McAllister et al. patent, which states that "RNA strands complementary to either one of the strands of the inserted DNA sequence" are produced by transcription. (Declaration of Dr. Sablon at ¶ 8.) According to Dr. Sablon, these flanking promoters are not the same. (Declaration of Dr. Sablon at ¶ 8.)

Dr. Sablon states that the rationale of using the vectors described in the McAllister et al. patent is that one can generate ***in vitro***, using the appropriate phage RNA polymerase, either sense or antisense transcripts from the same vector. (Declaration of Dr. Sablon at ¶ 9.) Because the purpose of the vectors described in the McAllister et al. patent is to generate synthetic RNA probes (see Background section, col. 1), it is crucial that only one strand becomes transcribed (either sense or antisense, but not both). (Declaration of Dr. Sablon at ¶ 10, emphasis in original.) According to Dr. Sablon, the transcription of only one strand can be brought about by one of two methods. First, one can linearize the vector with a particular restriction endonuclease that cuts between the insert and one of the flanking promoters in order to ensure transcription of only one strand, as is typically the case when both flanking promoters are of the same type. (Declaration of Dr. Sablon at ¶ 10.) Second, for vectors in which the two flanking promoters are of different origin, one can use only one promoter-specific phage RNA polymerase in the *in vitro* transcription reaction. (Declaration of Dr. Sablon at ¶ 10.)

Thus Dr. Sablon states that the vectors described in the McAllister et al. patent were clearly not intended to simultaneously produce transcripts from both directions. (Declaration of Dr. Sablon at ¶ 11.)

On page 5 of the Office Action, the Examiner stated that: "the vector system of McAllister et al. can produce the sense orientation DNA sequence and at the same [*sic*, same time] can produce the antisense ... orientation DNA sequence, thereby being capable of simultaneously transcribing both RNA 'strands' of the inserted DNA sequence." For the purposes of commenting on the Examiner's statement, Dr. Sablon assumed that the Examiner meant to indicate that the McAllister vectors are capable of producing sense and antisense orientation RNA sequences by transcription of both DNA "strands" of a DNA sequence inserted in the McAllister vectors. (Declaration of Dr. Sablon at ¶ 12.) Dr. Sablon disagrees with the Examiner's statement that the McAllister vectors are capable of producing sense and antisense orientation RNA sequences by transcription of both strands of an inserted DNA sequence, because this cannot be concluded from the McAllister et al. patent. (Declaration of Dr. Sablon at ¶ 13.) Specifically, Dr. Sablon states that there is nothing in the McAllister et al. patent to suggest to the skilled person that double stranded RNA could be made. (Declaration of Dr. Sablon at ¶ 14.) The McAllister patent methods use of the vectors for synthesizing RNA probes of high sensitivity. (Declaration of Dr. Sablon at ¶ 14.) Dr. Sablon confirms that RNA probes are known to the skilled person to be single-stranded. (Declaration of Dr. Sablon at ¶ 14.)

However, in contrast to the vectors described in the McAllister et al. patent, the above-identified application describes the use of bidirectional expression vectors for *in vivo* generation in *E. coli* of double stranded RNA. (Declaration of Dr. Sablon at ¶ 15.) According to Dr. Sablon, such a use would not have been suggested to the person of ordinary skill in the art by the McAllister et al. patent for the reasons stated above. (Declaration of Dr. Sablon at ¶ 15.) Moreover, this type of vectors, having opposite RNA polymerase promoters, has been well known to and universally used by molecular biologists since the mid 1980s, when Dr. Sablon was performing his PhD. (Declaration of Dr. Sablon at ¶ 15.) The use of this type of vectors for "*in vitro*" production of both strands (ds) RNA in a microorganism was not even anticipated by any molecular biologist at that time, not until the discovery thereof by the inventors of the present invention in the late 1990s. (Declaration of Dr. Sablon at ¶ 15.)

The vectors recited in the instant claims are used for producing double stranded RNA *in vivo*. Thus, McAllister fails to describe an element of the claimed invention, and none of the other cited reference provide this missing element. Accordingly, the cited combination of references does not provide all of the elements of the claimed invention, and thus the cited combination of references does not render the claimed invention obvious.

Motivation to combine the cited references is lacking

The skilled person would not have been motivated to introduce the plasmid of McAllister into the organism of Timmons, or to modify the Timmons expression vector. The Examiner's stated motivation for doing so is contrary to the stated use provide in McAllister, e.g., to produce single stranded RNA probes. Thus the skilled person would not have used the expression plasmid of McAllister in the bacteria of Timmons. See Declaration of Dr. Sablon at ¶¶ 8-15 in support of the lack of motivation of the skilled person.

No expectation of success

Dr. Sablon concludes that the person of ordinary skill in the art would not have had a reasonable expectation of success, based on the cited combination of prior art references, of practicing the invention claimed in the present application, of using the type of vectors known in the art to express double stranded RNA "inside" a microorganism, feeding such a microorganism that expresses the double stranded RNA "inside" its cell wall to *C. elegans*, and exerting an effect, from the inner content of the bacterium towards the cell cytoplasm of *C. elegans* cells. (Declaration of Dr. Sablon at ¶ 22.)

As supported by the evidence provided in the Declaration of Dr. Sablon, the cited combination of references does not provide all of the elements of the claimed invention and does not provide motivation to combine the respective teachings of the cited references. Therefore,

Applicant respectfully requests that the Examiner withdraw the rejection made under 35 U.S.C. § 103.

2. The Examiner has maintained the rejection of claims 30-41, 70-74, and 80-83 under 35 U.S.C. § 103(a) as being unpatentable over Fire et al., Graham, Ely et al., and Talkad et al. for the reasons of record as set forth in the Office action mailed on December 7, 2009 and as stated in the Office Action. Applicant respectfully traverses the rejection.

The cited combination of references does not provide all of the elements of the claimed invention

Dr. Erwin Sablon states that he has reviewed the Fire provisional application (US 60/068,562) that Fire et al. (WO99/32619) claims priority to. (Declaration of Dr. Sablon at ¶ 18.) Dr. Sablon states that nowhere in the Fire provisional application does Fire et al describe a target inhibition method in *C. elegans* wherein there is simultaneous synthesis of two RNA strands in a bacterium using a vector that has a DNA sequence inserted between two bacteriophage polymerase promoters, to produce double stranded RNA in the bacterium for the target inhibition method in *C. elegans*. (Declaration of Dr. Sablon at ¶ 18, emphasis in original.)

The Fire provisional application describes on page 11 that "[t]he use and construction of an expression vector are known in the art", citing to several references from 1990 and 1991, and a 1997 PCT published application. The 1990 and 1991 references are standard laboratory manuals. Dr. Sablon stated that none of the plasmids described in the 1997 PCT application referenced in the Fire provisional application are used to produce RNA corresponding to both strands of a gene sequence in a bacterium. (Declaration of Dr. Sablon at ¶ 19.)

Dr. Sablon states that none of the references cited on page 11 of the Fire provisional application provide any description of a "target inhibition method" wherein a bacterium is used that harbors a plasmid that is producing RNA corresponding to both strands of a gene resulting in the

production of double stranded RNA without any human intervention. (Declaration of Dr. Sablon at ¶ 20.) The "target inhibition method" described in the Fire provisional application required human intervention to carry out *in vitro* transcription, including the following steps: cutting the plasmid with restriction enzymes (this must be done twice, to produce two plasmids that are capable of making only one RNA strand); purifying the two different cut plasmids; adding the respective bacteriophage polymerases to the two different purified cut plasmids; collecting the resulting single stranded RNA molecules obtained in separate polymerase reactions; and mixing the single stranded RNA molecules to obtain the double stranded RNA, which is then injected in *C. elegans* to obtain target inhibition in *C. elegans*. (Declaration of Dr. Sablon at ¶ 20.)

Thus, according to Dr. Sablon, the Examiner's statements that Fire describes a target inhibition method in *C. elegans* that uses the claimed invention, that is, by using an expression vector that synthesizes in a bacterium two separate complementary RNA strands that form an RNA duplex in the bacterium, wherein the synthesis of the two RNA strands is driven by bacteriophage polymerase promoters such as T3, T7 and SP6 promoters, is not supported in the Fire provisional application. (Declaration of Dr. Sablon at ¶ 21, emphasis added.)

The Examiner also includes the Graham patent in the combination of references cited. As argued above in the section responding to the rejection of claims 30-36, 39, 74, 80, and 83 as anticipated by Graham, in the constructs described in Graham "...each copy of said structural gene sequence is separately placed under the control of a promoter...." (Graham, claim 4, emphasis added.) In contrast, in the claimed invention, there is only one structural gene sequence, i.e., one copy of the gene, which is flanked by the promoters such that it is then operatively placed in a sense orientation under the control of a first promoter and (automatically) in an antisense orientation of a second promoter.

Thus Applicant respectfully submits that Graham does not provide an element of the claimed invention. As such, the rejection of the claims as obvious fails for the additional reason that the cited combination of references does not provide all of the elements of the claimed invention.

The Fire PCT application is not prior art to the claimed invention

The Examiner asserts that the Fire provisional application (US 60/068,562) supports the teachings of the Fire PCT application, which are asserted to include inhibiting "target gene expression in a cell with an expression vector that synthesizes and produces two separate complementary strands and form[ing] an RNA duplex inside the cell." (Office Action at page 8.) The Examiner asserts that claims 1, 14, 16, 20 and pages 11 and 13 of the Fire provisional application adequately supports these alleged teachings, which Applicant takes to mean that the Fire provisional application provides an adequate written description under 35 U.S.C. § 112, first paragraph. Applicant respectfully disagrees. There is nothing in the Fire provisional application that describes using a bacterium containing a plasmid that directs the expression of double stranded RNA in an organism that takes up the bacterium. None of the claims or specification pages cited by the Examiner describe such concepts.

The Fire provisional application, at the indicated locations, does not provide an adequate written description. Claim 1 recites introducing double stranded RNA into a cell to inhibit expression of a gene. Claim 14 recites that RNA has two separate complementary strands. Claim 16 recites synthesis of the two complementary strands and initiation of RNA duplex formation inside the cell. Claim 20 recites that an expression vector in a cell produces the RNA. Each of claims 14, 16 and 20 depend from claims 1-12, and thus these three claims fail to teach their individual recitations in combination with anything other than the recitations of claims 1-12. For example, the recitations of claims 16 and 20 are not combined – there is no teaching that the expression vector of claim 20 can be used in the synthesis step recited in claim 16. In fact, based on the knowledge in the art at that time, as evidenced by the Declaration of Dr. Sablon that is described above, the skilled person would not have even attempted to make this combination.

On page 11, the only recitation of the use of expression vectors is that "[t]he use and construction of an expression vector are known in the art", citing to several references from 1990

and 1991, and a 1997 PCT published application. As noted above, The 1990 and 1991 references are standard laboratory manuals and the 1997 PCT published application is directed to methods of transforming plant tissue using a bacterium such as *Agrobacterium tumefaciens*. As noted above, the plasmids described on pages 4-5 of this PCT application contain different genes (one gene of interest and one antibiotic resistance gene for selection) driven by different promoters. None of the plasmids described in this PCT application are used to produce RNA corresponding to both strands of a gene sequence. (Declaration of Dr. Sablon at ¶ 19.) Therefore none of the references cited on page 11 of the Fire provisional application provide any description of a plasmid that could be used in producing RNA corresponding to both strands of a gene for the production of double stranded RNA.

On page 13, following a lengthy list of tumor types, the Fire provisional application states, *in reference to certain prior art references*, that "[i]ntroduction of RNA into cells can be used in certain biological systems to interfere with function of an endogenous gene." (emphasis added) No further description of the method of introducing the RNA, or any other aspect of the invention later claimed in the Fire PCT application, is provided. Thus the recitation on page 13 of the Fire provisional application does not contribute to an adequate written description of that which the Examiner alleges to be "target gene expression in a cell with an expression vector that synthesizes and produces two separate complementary strands and form[ing] an RNA duplex inside the cell." (Office Action at page 8.)

Therefore, Applicant respectfully submits that the Fire provisional application does not provide an adequate written description of the recitation that the Examiner alleges for the Fire PCT application. Accordingly, the Fire PCT application does not have an effective priority date that is prior to the effective filing date of Applicant. As such, the Fire PCT application is not prior art to the instant claims, and therefore the rejection of the claims as obvious over this cited combination of references fails.

Motivation to combine the cited references is lacking

Finally, the Examiner states on page 10 of the Office Action that motivation exists to combine the cited references because the expression vectors of Graham and Fire are "art-recognized equivalents". It clearly is not the case that the expression vectors of Graham and Fire are "art-recognized equivalents", based on the citation in the Fire priority application of standard laboratory manuals for a description of expression vectors as compared to Graham, which provides expression vectors deemed by the USPTO to be novel and inventive over the prior art, including those vectors referenced in the Fire provisional application.

No expectation of success

Dr. Sablon concludes that the person of ordinary skill in the art would not have had a reasonable expectation of success, based on the cited combination of prior art references, of practicing the invention claimed in the present application, of using the type of vectors known in the art to express double stranded RNA "inside" a microorganism, feeding such a microorganism that expresses the double stranded RNA "inside" its cell wall to *C. elegans*, and exerting an effect, from the inner content of the bacterium towards the cell cytoplasm of *C. elegans* cells. (Declaration of Dr. Sablon at ¶ 22.)

In summary, the cited combination of references does not provide all of the elements of the claimed invention and does not provide motivation to combine the respective teachings of the cited references. Moreover, the Fire PCT application is not prior art to the claimed invention. Therefore, Applicant respectfully requests that the Examiner withdraw the rejection made under 35 U.S.C. § 103.

Double Patenting

1. Claims 30-40, 70-74, and 80-83 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-11 of copending Application No. 11/522,307.

Applicant respectfully requests reconsideration. Because claims 8-11 of copending Application No. 11/522,307 are not at present considered allowable, Applicant defers addressing this rejection until a later date.

2. Claims 30-40, 70-74, and 80-83 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 24-25 of copending Application No. 11/666,017.

Applicant respectfully requests reconsideration. Because claims 24-25 of copending Application No. 11/666,017 are not at present considered allowable, Applicant defers addressing this rejection until a later date.

3. Claims 30-40, 70-74, and 80-83 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 27-28 and 34-35 of copending Application No. 11/666,021.

Applicant respectfully requests reconsideration. Because claims 27-28 and 34-35 of copending Application No. 11/666,021 are not at present considered allowable, Applicant defers addressing this rejection until a later date.

4. Claims 30-41, 70-74, 80 and 83 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-39 of copending Application No. 12/055,607.

Applicant respectfully requests reconsideration. Because claims 34-39 of copending Application No. 12/055,607 are not at present considered allowable, Applicant defers addressing this rejection until a later date.

5. Claims 30-41, 70-74, 80 and 83 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-10 and 12 of copending Application No. 12/087,537.

Applicant respectfully requests reconsideration. Because claims 6-10 and 12 of copending Application No. 12/087,537 are not at present considered allowable, Applicant defers addressing this rejection until a later date.

6. Claims 30-41, 70-74, 80 and 83 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 26-27 of US Patent 7,358,069.

Applicant respectfully requests reconsideration. Claims 26-27 of US Patent 7,358,069 recite a DNA construct that produces double stranded RNA comprising first and second promoters in opposite orientation and a first transcription terminator operably linked to the first promoter. The present claims do not recite a terminator linked to a promoter, nor would it be obvious to obtain the present claims, which do not require a transcription terminator, based on the claims of US Patent 7,358,069.

As noted by the Examiner on page 12 of the Office Action, due to the open language used in the claims, the instant claims do not require a transcription terminator. The Examiner has not provided a sound basis on which to reject the claims as obvious over claims 26 and 27 of US Patent 7,358,069. Because claims 26 and 27 require the presence of a transcription terminator based on the dependence from claim 1 of US Patent 7,358,069, these claims teach that such an element is required. The instant claims, as noted, do not require such an element, which would not be obvious over claims 26 and 27 of US Patent 7,358,069, which do require such an element.

Moreover, the present claims are further differentiated from the claims of US Patent 7,358,069 in that the present claims do include a DNA sequence between the promoters and recite that the promoters initiate transcription of the DNA sequence to produce double stranded RNA upon binding of a transcription factor to the promoters. Further, the claim recite that the expression vector comprises two identical promoters flanking the DNA sequence. Neither of these features are recited in claims 26 and 27 of US Patent 7,358,069, and thus the present claims are not obvious over claims 26 and 27 of US Patent 7,358,069.

Thus the claims are patentably distinct and should not be subjected to an obviousness-type double patenting rejection over claims 26-27 of US Patent 7,358,069.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If a fee is due, please charge our Deposit Account No. 23/2825 under Docket No. D0590.70011US02 from which the undersigned is authorized to draw.

Dated: December 28, 2010

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